Amendments to the Specification:

Please replace the original paper copy of the Sequence Listing with the substitute paper copy of the Sequence Listing filed herewith.

At page 1, line 1, please delete subheading:

~~DESCRIPTION~~

Please amend the title to read as:

AGONIST ANTIBODIES AGAINST HETEROMERIC RECEPTORS

Please insert the following paragraph after the title:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is the National Stage of International Application No. PCT/JP2003/015230, filed November 28, 2003, which claims the benefit of Japanese Patent Application Serial No. 2002-377078, filed on December 26, 2002. The contents of both applications are hereby incorporated by reference in their entireties.

Please replace the paragraph beginning at page 17, line 19, with the following amended paragraph:

PolyA(+) RNA was extracted from the spleens of immunized mice, and scFv was then synthesized by RT-PCR. A ~~plasmid~~ phage library was constructed that expresses scFv as a fusion protein with the product of the f1 phage gene 3 (J. Immun. Methods, 201, (1997), 35-55). An E. coli library (2 x 10^9 cfu) was inoculated to 50 ml of 2x YTAG (2x TY containing 100 μg/ml ampicillin and 2% glucose), and the culture was incubated at 37°C until OD_{600} reached 0.4-0.5. 4 x10^{11} helper phage VCSM13 were added, and the culture was allowed to stand for 15 minutes at 37°C to be infected. 450 mL of 2x YTAG and 25 μl of 1 mol/l IPTG were added to the culture, and incubated at 26°C for ten hours. The culture supernatant was collected by

centrifugation. 100 ml of PEG-NaCl (10% polyethylene glycol 8000 and 2.5 mol/l NaCl) was combined with the supernatant, and allowed to stand at 4°C for 60 minutes. Phages were precipitated by centrifugation at 10,800x g for 30 minutes. The precipitate was suspended in 40 ml of water, and mixed with 8 ml of PEG-NaCl, then allowed to stand at 4°C for 20 minutes. Phages were precipitated by centrifugation at 10,800x g for 30 minutes. The precipitate was suspended in 5 ml of PBS. AR1FLAG and AR2FLAG were labeled with biotin using No-Weigh Premeasured NHS-PEO4-Biotin Microtubes (Pierce). 100 pmol of biotin-labeled AR1FLAG or AR2FLAG was added to the phage library. The antigen was contacted with the phages for 60 minutes. 600 μl of Streptavidin MagneSphere (Promega), which was washed with 5% M-PBS (PBS containing 5% skimmed milk), was added, and allowed to bind to the antigen for 15 minutes. The beads were washed three times with 1 ml of PBST (PBS containing 0.1% Tween-20) and then three times with PBS. The beads were suspended in 0.8 ml of 0.1 mol/l glycine/HCl (pH 2.2) for five minutes to elute the phages. The collected phage solution was neutralized by adding 45 μl of 2 mol/l Tris. The phage solution was added to 10 ml of XL1-Blue culture during the logarithmic growth phase (OD_{600} of 0.4-0.5), and allowed to stand at 37°C for 30 minutes for infection. The culture was spread on 2x YTAG plates, and then incubated at 30°C. Colonies were collected and inoculated to 2x YTAG, and then incubated at 37°C until OD_{600} reached 0.4-0.5. 5 μl of 1 mol/l IPTG and 10^{11} pfu of helper phage (VCSM13) were added to 10 ml of the culture liquid, and allowed to stand at 37°C for 30 minutes. The bacterial cells were collected by centrifugation, and then re-suspended in 100 ml of 2x YTAG containing 25 μg/ml kanamycin. The suspension was incubated at 30°C for ten hours. The culture supernatant was collected by centrifugation and mixed with 20 ml PEG-NaCl, then allowed to stand at 4°C for 20 minutes. Phages were precipitated by centrifugation at 10,800x g for 30 minutes, and then re-suspended in 2 ml of PBS. The suspension was used in subsequent panning experiments. In the second-round panning, the beads were washed five times with PBST and then five times with PBS. The eluted phages were infected to E. coli cells, and clones producing AR-binding phages were selected from the resultant E. coli cells.

Please replace the paragraph beginning at page 19, line 6, with the following amended paragraph:

The expression vector pCAGGss-g4CH-hetero-IgG4 was constructed to express scFv-CH1-Fc. scFv can be inserted into the vector at the SfiI site, between intron-CH1-Fc (human IgG4 cDNA) and the human signal sequence driven by the CAGG promoter. With reference to IgG1 knobs-into-holes technology (Protein Engineering vol.9, 617-621, 1996, Nature Biotechnology vol.16, 677-681, 1998), the amino acids of the CH3 of IgG4 were substituted in order to express heteromeric molecules. Type A are Y349C and T366W mutants; and type B are E356C, T366S, L368A, and Y407V mutants. In addition, an amino acid was substituted in the hinge domain for both mutant types (from -ppcpScp- to -ppcpPcp-). Types A were constructed using the human IL-3 signal sequence, while types B were constructed using the human IL-6 signal sequence (pCAGG-IL3ss-g4CHPa and pCAGG-IL6ss-g4CHPb). PCR products, corresponding to the scFv regions of the clones selected based on their nucleotide sequences, were treated with SfiI. The products from the anti-AR1 clones were subcloned into pCAGG-IL3ss-g4CHPa, and those from the anti-AR2 clones were subcloned into pCAGG-IL[[3]]6ss-g4CHPb. Expression vectors for each of the 2025 combinations of the 45 anti-AR1 clones and 45 anti-AR2 clones were transfected into HEK293 cells using lipofectamine 2000. The culture supernatants were collected three days after transfection.